Annals of Clinical and Analytical Medicine
Original Research

Percentage of Human Chorionic Gonadotropin change in the forty-eight hours prior to methotrexate injection in predicting treatment success

Erhan Akturk[1], Murat Ibrahim Toplu[1], Cagdas Nurettin Emeklioglu[1], Tugba Salman[1], Fatma Nur Cetinkaya[1], Simten Genc[1], Arzu Yurci[2], Veli Mihmanli[1]
[1] Department of Obstetrics and Gynecology, Prof. Dr. Cemil Taşçıoğlu City Hospital
[2] Department of IVF and Reproductive Health Center, Bahcelievler Memorial Hospital, Istanbul, Turkey

Abstract

Aim: Although many reports that examine the concentration of β-hCG are available, there is a limited number of articles in the literature about the dynamics of β-hCG. Our aim in this study was to reveal the role of β-hCG percentage change before methotrexate injection on predicting treatment success.

Material and Methods: This retrospective study was conducted between May 2015 and February 2019 at the gynecology department of a tertiary hospital. Medical data of patients who were diagnosed with tubal ectopic pregnancy were reviewed (n:1073). The percentages of β-hCG change between 48 hours before methotrexate injection and day 1 were compared between the failure and success groups. The ROC curve was designed to determine the optimal β-hCG change percentage to predict treatment success.

Results: Four hundred and thirty-four patients were eligible for methotrexate treatment. The median value of β-hCG percentage change before methotrexate injection was significantly higher in the failure group (+13.7(+9.04/+17.68)) compared to the success group (+8.62(+5.8/+11.5)) (p<0.001). The area under the curve was 0.727 with 95% CI(0,659-0,795) (p<0,01). With the cutoff value of 11.27%, sensitivity, specificity, PPV and NPV were 71,2%, 73,4%, 35% and 93%, respectively.

Discussion: Along with HCG concentrations, HCG dynamics should also be investigated as to whether it has a role in the prediction of methotrexate success. We think that utilizing β-hCG dynamics as an additional tool in the prediction of methotrexate treatment outcome should be considered in every case of tubal ectopic pregnancy.

Keywords

Tubal Ectopic Pregnancy, Methotrexate, Beta Human Chorionic Gonadotropin

DOI: 10.4328/ACAM.21627 Received: 2023-01-30 Accepted: 2023-03-02 Published Online: 2023-03-06 Printed: 2023-03-25 Ann Clin Anal Med 2023;14(Suppl 1):S62-66
Corresponding Author: Cagdas Nurettin Emeklioglu, Department of Obstetrics and Gynecology, Prof. Dr. Cemil Taşçıoğlu City Hospital, Sisli, Istanbul, Turkey.
E-mail: c.n.emeklioglu@gmail.com P: +90 535 912 99 13
Corresponding Author ORCID ID: https://orcid.org/0000-0003-1859-8680
This study was approved by the Ethics Committee of Prof. Dr. Cemil Taşçıoğlu City Hospital (Date: 2019-03-19, No: 1197)

Introduction

Ectopic pregnancy is encountered in 1-2% of all pregnancies and is accepted as a life-threatening emergency [1]. It is one of the most dangerous titles regarding maternal mortality in the first trimester of pregnancy [2]. Transvaginal ultrasound, along with serial beta-human chorionic gonadotropin (β-hCG) measurements and a high index of suspicion, is the most used tool to detect ectopic pregnancy to prevent adverse consequences.

The goal is an early treatment to prevent tubal rupture, internal hemorrhage and maternal morbidity. Methotrexate treatment is considered a feasible solution in meticulously selected cases [3]. Stovall's "single dose protocol" is the most commonly preferred one among the methotrexate treatment protocols [4].

Treatment failure risk should be taken into account and cases must be selected appropriately. Presence of fetal cardiac activity, free peritoneal blood, size (>4 cm) of the ectopic mass, high (>5,000 mIU/mL) initial β-hCG concentration, increasing β-hCG concentrations (>50% in 48 hours) before methotrexate, rapid rise of hCG concentrations after methotrexate are the predictive factors for methotrexate failure [5-7]. The documented success rate of treatment in the "single dose protocol" is between 75,45% and 87% [8,9]. Serial β-hCG measurements before methotrexate treatment are efficient to discriminate actual ongoing ectopic pregnancies from spontaneously resolving ones [10]. Presumably, successive β-hCG measurements may detect spontaneous resolution in more than 60% of the cases [11].

Since β-hCG rise before methotrexate treatment might indicate trophoblastic tissue activity, we tried to delineate whether β-hCG percentage change can predict the methotrexate success or not. The role of β-hCG levels on day 1 and 48 hours prior to the methotrexate injection in predicting success was the secondary outcome. Finally, determining a percentage change cutoff value with optimal sensitivity and specificity to predict treatment success was our tertiary outcome.

Material and Methods

This retrospective study was conducted in accordance with the Principles of the Declaration of Helsinki and approved by our local ethics committee (Date: 2019-03-19, No: 1197). Between May 2015 and February 2019, 434 tubal ectopic pregnancy cases who had attended to our gynecology department were included in this study.

Medical data of women who were diagnosed with tubal ectopic pregnancy were reviewed (n:1073). Age, gravidity, parity, date of the last normal menstrual period, body mass index (BMI), day 1 β-hCG and β-hCG at 48 hours prior to the methotrexate injection of all eligible cases were recorded. Tubal ectopic pregnancy diagnosis had been established on both β-hCG level measurements and a transvaginal ultrasound indicating ectopic pregnancy via conforming an inhomogeneous mass next to the ovary, an extraovarian hyperechoic mass or an extrauterine gestational sac with a thin endometrium [12]. Patients presenting with hemodynamic instability, β-hCG levels above 10,000 IU, fetal pole with cardiac activity, severe abdominal pain, or signs of intra-abdominal haemorrhage had been treated surgically (n:238), so they were excluded. Cases that showed spontaneous resolution (n:370), and thirty- one subjects with insufficient data were also excluded. As a result, 434 cases were eligible for the study. Patients are were dievided into two groups according to methotrexate treatment outcome: success group and failure group. As a result, 361 subjects were in the success group, whereas 73 cases were in the failure group.

Single dose protocol had beenwas used in all cases at a dose of 50 mg/m2 [13]. Methotrexate administration day was defined as day 1, and β-hCG measurements were repeated on days 4 and 7 in an inpatient or outpatient setting. Treatment failure had beenwas defined as having symptoms of tubal rupture or β-hCG not falling more than 15% between days 4 and day 7. Treatment success had beenwas defined as recovery.

In this study, we aimed Our aim was to reveal the role of β-hCG percentage change before methotrexate injection oin predicting treatment success. The percentages of β-hCG change between 48 hours before methotrexate injection and day 1 were compared between the 'failure group' and the 'success group'. The Eequation of β-hCG percentage change was as follows:

βhCG change (%)=(βhCG day 1-HCG 48 hours prior to injection)/ (βhCG 48 hours prior to injection) x100

Additionally, success and failure groups were compared regarding to both the β-hCG level on day 1 and the β-hCG level 48 hours before methotrexate injection. A receiver-operating characteristic curve was designed to determine the optimal β-hCG level change for treatment success.

Statistical analysis

All analysis was performed using SPSS software (Statistical Package for the Social Sciences, version 25.0, SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to evaluate the eligibility of the data for normal distribution. Descriptive statistical methods were used to evaluate frequency, percentage, mean (standard deviation (SD)), median (25th and 75th percentiles) when appropriate. The Chi-square test was used for categorical variables. Student t- test was applied for normally distributed data and mean (standard deviation (SD)) was used as the descriptive statistical method. On the other hand, the Mann-Whitney U test was applied for non-normal data, and the median (25^{th} and 75^{th} percentiles) was used as the descriptive statistical method. Finally, a receiver-operating characteristic curve was utilizsed to establish the optimal cutoff value of β-hCG change with the highest sensitivity and specificity for treatment success. A p-P value of less than 0.05 was considered significant.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

In our study, there were 1073 subjects diagnosed with tubal ectopic pregnancy. Of these, 434 patients (40%) were eligible for methotrexate treatment after excluding subjects that got immediate surgery (n:238), those that resolved spontaneously (n:370) and those that had insufficient data (n:31) (Figure 1). Characteristics of variables in the treatment success and treatment failure groups are depicted in Table 1. Difference between the two groups regarding age, gravidity, parity, BMI and gestational week did not reach statistical significance. There was no significant statistical difference regarding day

1 β-hCG levels and β-hCG levels 48 hours before methotrexate injection between the groups (Table 2).

The percentages of β-hCG change between 48 hours before methotrexate injection and day 1 were compared between the 'failure group' and the 'success group'. The median value of β-hCG percentage change before methotrexate injection was significantly higher in the failure group (+13.7(+9.04/+17.68)) compared to the success group (+8.62(+5.8/+11.5)) (p<0.001). A receiver-operating characteristic curve was established to determine the optimal β-hCG percentage change for treatment outcome. The area under the curve was 0.727 with 95% CI(0,659-0,795) (p<0,01) (Figure 2). With the cutoff value of 11,27%, the characteristics of the model to predict treatment success were as follows: sensitivity: 71.2%, specificity: 73.4%, diagnostic accuracy: 73%, negative predictive value (NPV): 93%, and positive predictive value (PPV): 35%.

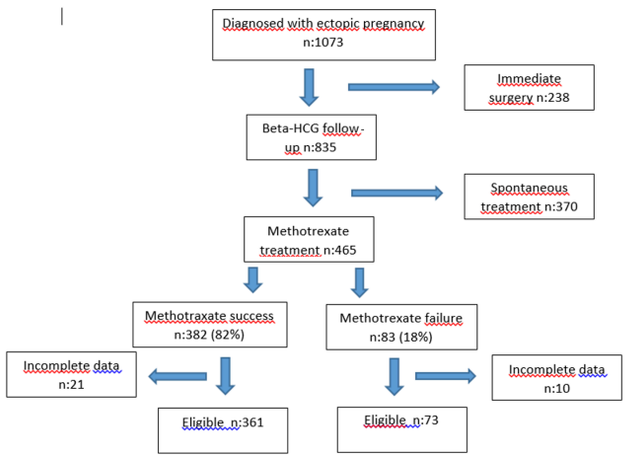

Figure 1. Flow chart of ectopic pregnancy patients.

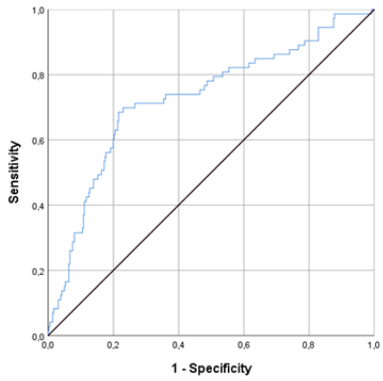

Figure 2. Receiver operating characteristic (ROC) curve for HCG change in the 48 hours before methotrexate injection as a predictor for treatment success (area under the curve: 0.727 with 95% CI(0,659-0,795) (p<0,01)).

Table 1. Comparison of patient characteristics between the two groups.

	Success group n:361	Failure group n:73	P-value
Age (mean (SD))	27.72(6.28)	27.08(6.43)	0.431[1]
Parity (median (25th-75th percentiles))	1 (0-2)	1 (0-2)	0.82[2]
Gravida (median (25th-75th percentiles))	2 (2-4)	2 (1-4)	0.44[2]
BMI (mean (SD))	25.04(4.18)	24.1(4.3)	0.081[1]
Gestational week (median (25th-75th percentiles))	5.9(5.5-6.4)	6 (5.6-6.4)	0.27[2]

SD: Standard Deviation, BMI: Body Mass Index; [1]Student t-test, [2]Mann-Whitney U test

Table 2. Comparison of HCG levels between the two groups.

	Success group n:361	Failure group n:73	P-value
β-hCG, day 1 (mU/ml) (mean (SD))	2515.7(1775)	2804.1(2022)	0.327[1]
β-hCG, 48 hours prior to methotrexate (mU/ml) (mean(SD))	2295.5(1612)	2451.8(1764)	0.634[1]
β-hCG change (%) (median (25th/75th percentiles))	+8.62(+5.8/+11.5)	+13.7(+9.04/+17.68)	<0.01[2]

β-hCG: Human Chorionic Gonadotropin; [1]Student t-test, [2]Mann-Whitney U test

Discussion

If patients diagnosed with tubal ectopic pregnancy are not eligible for the expectant management, medical management is acceptable as a plausible alternative for surgery. Methotrexate therapy is the most used pharmacologic treatment for hemodynamically stable patients due to its safety and efficacy [14]. It is of paramount importance to select appropriate patients prior to medical intervention, since patient compliance for follow-up is crucial and treatment failure risk is always present [15]. Methotrexate success for the single dose protocol is reported as a more than a 15% decline in β-hCG levels between days 4 and 7 following methotrexate injection, with a PPV of 93% [16]. Furthermore, this decline was reported as 88-100% indicating treatment success [17,18].

Although β-hCG patterns for ongoing intrauterine pregnancies and resolving pregnancies are well understood, there is no tool or model that can efficaciously specify a β-hCG curve for ectopic pregnancies [19]. In the literature, there are several studies researching β-hCG as a marker for trophoblastic cell activity. Ferreira et al. demonstrated a direct correlation between increased levels of serum β-hCG during the 48 hours prior to surgery with higher trophoblastic cell proliferation and angiogenesis in tubal pregnancy [20]. Oktay et al assessed salpingectomy specimens of tubal ectopic pregnancies for the presence or absence of myosalpingeal invasion and obtained higher serum β-hCG levels in patients having muscular layer trophoblastic invasion compared to the group having no trophoblastic invasion of the muscular layer (13 665 ± 2986 mIU/ml and 2169 ± 870 mIU/ml, respectively; P = 0.0001) [21]. A serum β-hCG cutoff level of 5400 mIU/ml or higher had an 89% PPV and 94% NPV value for the detection of invasion [21]. Pulatoglu et al. indicated that the cutoff β-hCG value, detecting the failure of methotrexate injection with 71.8% sensitivity and 68.2% specificity, was 1362 mIU/mL. In cases having β-hCG

levels more than 1362 mIU/mL, the failure rate was 23.9%, while at lower values, the failure rate was 17.9% [22]. This did not reach statistical significance [22]. In our study, there was no difference regarding day1 β-hCG levels and β-hCG value 48 hours before methotrexate injection between the success and failure groups.

Along with HCG concentrations, HCG dynamics should also be investigated as to whether it has a role in the prediction of methotrexate success. Dudley et al. reported that there was a significant increase in the β-hCG change both before and after methotrexate injection in ectopic pregnancies that resulted in rupture: +0.94 vs. +0.16 and +0.38 vs. -0.21 ($p<0.01$), respectively [23]. In their 401-patient retrospective study, Cohen et al reported that β-hCG percentage change in the 48 hours preceding MTX injection and β-hCG concentration at day 1 were independent predictors for tubal rupture (odds ratio [OR] = 1.08, 95% confidence interval [CI] = 1.04-1.12, $p < 0.001$ for every percentage change in β-hCG; OR = 1.001, 95% CI = 1.0003-1.002 for every unit change in β-hCG, respectively) [24]. They concluded that in women with β-hCG percentage increment more than 69% in the 48 hours prior to injection, the probability for tubal rupture was 85% [24]. They also indicated that the absolute risk for tubal rupture in women with β-hCG increment of less than 20% is low [24]. In another study, da Costa Soares et al investigated the role of β-hCG increment before methotrexate injection as a success predictor [25]. In their study, the mean β-hCG increment in the methotrexate failure group was significantly higher than in the success group (36% vs. 13%, respectively). By using ROC curve analysis, the optimal cut-off value for success was 11.1% [25]. Similarly, in our present study, the median value of β-hCG percentage change before methotrexate injection was significantly higher in the failure group (+13.7(+9.04/+17.68)) compared to the success group (+8.62(+5.8/+11.5)). When we used ROC curve analysis, the optimal cut-off value for success was 11.27% with a sensitivity of 71,2, which was comparable to that of da Costa Soares [25]. Besides, we obtained a PPV of 35% which is low. In other words, a woman with a positive result in favor of failure, has a 35% chance of failing treatment. On the other hand we obtained an NPV of 93% which is high. In other words, the proportion of the cases giving negative results (methotrexate success prediction) who are really in the success group is 93%. With this aspect, our model with an 11.27% cutoff is stronger in predicting success than in predicting failure. We think that utilizing β-hCG dynamics as an additional tool in the prediction of methotrexate treatment outcome should be considered in every case of tubal ectopic pregnancy.

Study Limitations

A limitation of this study is its retrospective nature. Prospective studies should be conducted to predict methotrexate treatment outcome. In addition, during the study period decisions regarding intervention were based on clinical judgment by different physicians.

Conclusion

In conclusion, β-hCG increment before methotrexate injection is a valuable predictor for methotrexate treatment success. Patients with β-hCG increment less than 11,27% can be reassured for treatment success with an NPV of 93% irrespective of serum β-hCG concentration.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: *None*

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

References

1. Panelli DM, Phillips CH, Brady PC. Incidence, diagnosis and management of tubal and nontubal ectopic pregnancies: a review. Fertil Res Pract. 2015;1:15.

2. Creanga AA, Shapiro-Mendoza CK, Bish CL, Zane S, Berg CJ, Callaghan WM. Trends in ectopic pregnancy mortality in the United States: 1980-2007. Obstet Gynecol. 2011;117(4):837-43.

3. Alur-Gupta S, Cooney LG, Senapati S, Sammel MD, Barnhart KT. Two-dose versus single-dose methotrexate for treatment of ectopic pregnancy: a meta-analysis. Am J Obstet Gynecol. 2019;221(2):95-108.e2.

4. Kanmaz AGK, Hamdi İnan A, Beyan E, Budak A. Various BhCG monitoring protocols for predicting the success of single-dose methotrexate in the treatment of ectopic pregnancy. J Obstet Gynaecol. 2019;39(6):811-15.

5. Bonin L, Pedreiro C, Moret S, Chene G, Gaucherand P, Lamblin G. Predictive factors for the methotrexate treatment outcome in ectopic pregnancy: A comparative study of 400 cases. Eur J Obstet Gynecol Reprod Biol. 2017;208:23-30.

6. Pulatoglu C, Dogan O, Basbug A, Kaya AE, Yildiz A, Temizkan O. Predictive factors of methotrexate treatment success in ectopic pregnancy: A single-center tertiary study. North Clin Istanb. 2018;5(3):227-31.

7. Rabischong B, Tran X, Sleiman AA, Larraín D, Jaffeux P, Aublet-Cuvelier B, et al. Predictive factors of failure in management of ectopic pregnancy with single-dose methotrexate: a general population-based analysis from the Auvergne Register, France. Fertil Steril. 2011;95(1):401-4.e1.

8. Sindiani AM, Alshdaifat E, Obeidat B, Obeidat R, Rawashdeh H, Yaseen H. The Use of Single Dose Methotrexate in the Management of Ectopic Pregnancy and Pregnancy of Unknown Location: 10 Years' Experience in a Tertiary Center. Int J Womens Health. 2020;12:1233-39.

9. Gungorduk K, Asicioglu O, Yildirim G, Gungorduk OC, Besimoglu B, Ark C. Comparison of single-dose and two-dose methotrexate protocols for the treatment of unruptured ectopic pregnancy. J Obstet Gynaecol. 2011;31(4):330-4.

10. Cohen A, Zakar L, Gil Y, Amer-Alshiek J, Bibi G, Almog B, et al. Methotrexate success rates in progressing ectopic pregnancies: a reappraisal. Am J Obstet Gynecol. 2014;211(2):128.e1-5.

11. Levin I, Tsafrir Z, Sa'ar N, Lessing, J, Avni, A, Gamzu, R. et al. "Watchful waiting" in ectopic pregnancies: a balance between reduced success rates and less methotrexate. Fertil Steril. 2011;95(3):1159-60.

12. van Mello NM, Mol F, Ankum WM, Mol BW, van der Veen F, Hajenius PJ. Ectopic pregnancy: how the diagnostic and therapeutic management has changed. Fertil Steril. 2012;98(5):1066-73.

13. Practice Committee of American Society for Reproductive Medicine. Medical treatment of ectopic pregnancy: a committee opinion. Fertil Steril. 2013;100(3):638-44.

14. Mohammad NS, Nazli R, Zafar H, Fatima S. Effects of lipid based Multiple Micronutrients Supplement on the birth outcome of underweight pre-eclamptic women: A randomized clinical trial. Pak J Med Sci. 2022;38(1):219-26.

15. Sivalingam VN, Duncan WC, Kirk E, Shephard LA, Horne AW. Diagnosis and management of ectopic pregnancy. J Fam Plann Reprod Health Care. 2011;37(4):231-40.

16. Kirk E, Condous G, Van Calster B, Haider Z, Van Huffel S, Timmerman D, et al. A validation of the most commonly used protocol to predict the success of single-dose methotrexate in the treatment of ectopic pregnancy. Hum Reprod. 2007;22(3):858-63.

17. Skubisz MM, Li J, Wallace EM, Tong S. Decline in βhCG levels between days 0 and 4 after a single dose of methotrexate for ectopic pregnancy predicts treatment success: a retrospective cohort study [published correction appears in BJOG. BJOG. 2011;118(13):1665-8.

18. Nguyen Q, Kapitz M, Downes K, Silva C. Are early human chorionic gonadotropin levels after methotrexate therapy a predictor of response in ectopic pregnancy? Am J Obstet Gynecol. 2010;202(6):630.e1-5.

19. Silva C, Sammel MD, Zhou L, Gracia C, Hummel AC, Barnhart K. Human chorionic gonadotropin profile for women with ectopic pregnancy. Obstet

Gynecol. 2006;107(3):605-10.
20. Ferreira DF, Elito Júnior J, Araujo Júnior E, Stavale JN, Camano L, Moron AF. Trophoblastic infiltration in tubal pregnancy evaluated by immunohistochemistry and correlation with variation of Beta-human chorionic gonadotropin. Patholog Res Int. 2014;2014:302634.
21. Oktay K, Brzyski RG, Miller EB, Krugman D. Association of serum beta-hCG levels with myosalpingeal invasion and viable trophoblast mass in tubal pregnancy. Obstet Gynecol. 1994;84(5):803-6.
22. Pulatoglu C, Dogan O, Basbug A, Kaya AE, Yildiz A, Temizkan O. Predictive factors of methotrexate treatment success in ectopic pregnancy: A single-center tertiary study. North Clin Istanb. 2018;5(3):227-31.
23. Dudley PS, Heard MJ, Sangi-Haghpeykar H, Carson SA, Buster JE. Characterizing ectopic pregnancies that rupture despite treatment with methotrexate. Fertil Steril. 2004;82(5):1374-8.
24. Cohen A, Bar-On S, Cohen Y, Sandel O, Fouks Y, Michaan N, et al. Ruptured ectopic pregnancies following methotrexate treatment: clinical course and predictors for improving patient counseling. Reprod Sci. 2022;29(4):1209-14.
25. da Costa Soares R, Elito J Jr, Camano L. Increment in beta-hCG in the 48-h period prior to treatment: a new variable predictive of therapeutic success in the treatment of ectopic pregnancy with methotrexate. Arch Gynecol Obstet. 2008;278(4):319-24.

How to cite this article:
Erhan Akturk, Murat Ibrahim Toplu, Cagdas Nurettin Emeklioglu, Tugba Salman, Fatma Nur Cetinkaya, Simten Genc, Arzu Yurci, Veli Mihmanli. *Percentage of Human Chorionic Gonadotropin change in the forty-eight hours prior to methotrexate injection in predicting treatment success. Ann Clin Anal Med 2023;14(Suppl 1):S62-66*

This study was approved by the Ethics Committee of Prof. Dr. Cemil Taşçıoğlu City Hospital (Date: 2019-03-19, No: 1197)